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Carotid Intima-Media Thickness Is Associated With Premature Parental Coronary Heart Disease

The Framingham Heart Study

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Background—A family history of coronary heart disease (CHD) is an independent risk factor for cardiovascular events. However, the mechanisms underlying this susceptibility have not been fully elucidated. We hypothesized that an important mediator of the familial predisposition to CHD is subclinical atherosclerosis, which is detectable by noninvasive imaging.

Methods and Results—We studied 1662 subjects (mean age 57, 51% women) in the Framingham Offspring Study who underwent carotid ultrasonography and had both biological parents in the original (parental) cohort. Parental CHD events were validated prospectively by a physician endpoint committee. The associations of carotid intima-media thickness (IMT) with premature parental CHD (occurring before age 60) and any parental CHD (no age restriction) were examined in age- and multivariable-adjusted analyses. Age-adjusted mean internal carotid IMT was higher in subjects who had at least one parent with premature CHD than in those without a validated parental history of premature CHD (men 1.13 versus 1.04 mm, $P < 0.01$; women 0.92 versus 0.85 mm, $P = 0.03$). In both sexes, these differences remained significant after adjustment for cardiovascular risk factors. In analyses without a restriction on parental age of CHD onset, the association between carotid IMT and parental CHD was not statistically significant. There was also no significant association of common carotid IMT with premature or any parental CHD.

Conclusions—These findings suggest that subclinical atherosclerosis, assessed in the carotid arteries, is more prevalent in individuals with a family history of CHD. Early-onset parental CHD, in particular, identifies offspring with a strong familial predisposition to atherosclerosis. (*Circulation*. 2003;108:572-576.)

Key Words: atherosclerosis ■ carotid arteries ■ genetics ■ epidemiology ■ risk factors

A family history of premature coronary heart disease (CHD) is an independent risk factor for cardiovascular events.¹⁻⁶ The mechanisms underlying this familial clustering have not been established, but may include an increased susceptibility to atherosclerosis,⁷ an increased tendency for thrombosis,⁸ or other factors. Important insight may be gained by understanding how offspring of parents with premature CHD differ from offspring of parents without premature CHD. Evidence supporting a higher burden of subclinical atherosclerosis in individuals with a parental history of premature CHD would implicate pathways involved in atherogenesis and point to the potential utility of subclinical disease measures as “intermediate phenotypes” for mapping CHD susceptibility genes.^{7,9,10} Elucidating this association may also have clinical implications, because it has

been suggested that asymptomatic adults with a positive family history may benefit from subclinical disease screening to determine need for primary preventive therapies.¹¹

High-resolution carotid ultrasound provides a noninvasive assessment of atherosclerotic burden. Increased intima-media thickness (IMT) is associated with prevalent coronary heart disease,^{12,13} peripheral vascular disease,¹⁴ and incident cardiovascular events.¹⁵ There is also evidence that carotid IMT may be a heritable trait.⁹ An association between carotid IMT or plaque and a parental history of CHD has been studied in one hospital-based study⁷ and several community-based studies.^{10,16,17} Potential limitations of prior studies include reliance on self-reported family history,^{10,16,17} limited attention to the influence of parental sex or age of disease onset,^{7,10,16} use of different IMT definitions,^{7,10,16} and modest statistical

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power.^{7,16} The use of self-reported family history, in particular, introduces the risk of spurious associations due to recall bias, because subjects at higher risk for cardiovascular disease may be more likely to report disease in their parents.

The Framingham Heart Study provides an opportunity to study the association between parental history and offspring subclinical atherosclerosis, using a population-based cohort of families in which CHD events have been validated prospectively in both parents and offspring. It is also possible to examine whether this association is modified by parental sex or age of disease onset, offspring sex, or offspring cardiovascular disease risk factors.

Methods

Subjects

The study design of the Framingham Heart Study has been detailed previously.^{18,19} The original study was initiated in 1948 with the recruitment of 5209 men and women for a long-term prospective study of cardiovascular risk factors. In 1971, 5124 offspring (and their spouses) of the original participants were recruited for the offspring study. Subjects in the original and offspring cohorts have been followed with biennial and quadrennial examinations, respectively.

The sixth offspring examination (1995–1998) was attended by 3532 participants, 3407 (96%) of whom underwent carotid ultrasonography. We limited the present investigation to the 1662 individuals who had both biological parents in the original cohort, in order to ensure complete ascertainment of parental CHD for all study subjects.

Clinical Evaluation

A medical history and physical examination were administered at each examination. A fasting lipid panel, which included total cholesterol and HDL cholesterol, was performed. Diabetes was defined by a fasting glucose ≥ 140 mg/dL or use of insulin or hypoglycemic medications.²⁰ Analyses using the more current fasting glucose threshold of 126 mg/dL were also performed.²¹ Persons were classified as current cigarette smokers if they reported cigarette smoking during the previous year. The protocol was approved by the Institutional Review Board of Boston Medical Center.

All cardiovascular events in the original and offspring cohorts were adjudicated by a panel of 3 physicians, based on a review of data collected from Framingham clinic visits, hospitalizations, and office records.²² The definition of CHD included myocardial infarction (recognized or unrecognized), stable angina, coronary insufficiency, or CHD death. CHD was considered to be premature if it occurred before the age of 60.²³

Carotid Ultrasonography

Imaging was conducted with a 7.5 MHz transducer for the common carotid artery and a 5.0-MHz transducer for the carotid bulb and internal carotid artery (Toshiba Medical Systems).^{15,24} Images were obtained at the level of the distal common carotid artery, the carotid artery bulb, and the proximal 2 cm of the internal carotid artery. Measurements were made by a single sonographer and over-read by one of the investigators (JFP); both were blinded to clinical information, including parental disease status.

IMT measurements were made at each of the 3 sites on both sides. For each site, the maximal IMT measurements in the near and far walls were averaged. Internal carotid IMT was defined as the mean of the maximal IMT measurements for the carotid artery bulb and the internal carotid artery on both sides. Common carotid IMT was defined as the mean of the maximal IMT measurements for the right and left common carotid arteries. Images were gated to diastole.

Statistical Analyses

Bivariate analyses were performed comparing the age-adjusted mean IMT in subjects with and without parental CHD. For the parental history categories, we used both premature CHD and overall CHD in separate analyses. Analyses were also performed separately for internal carotid IMT and common carotid IMT.

To examine whether the effect of family history was explained by familial clustering of cardiovascular risk factors, additional analyses were performed in which the mean IMT values were adjusted for risk factor levels using the least squares method. Risk factors included blood pressure variables (systolic blood pressure, pulse pressure, use of anti-hypertensive therapy), cholesterol variables (total and HDL), smoking, body mass index, and diabetes. Because IMT values were skewed, we repeated the above analyses with log transformation of IMT values. We also repeated the analyses using a generalized estimating equations approach to account for possible nonindependence of the observations due to familial correlations within the study sample.

In secondary analyses, we examined whether the sex of the parent with CHD was important, by separating individuals with CHD in one parent into those with maternal CHD and those with paternal CHD. In these analyses, those having CHD in both parents were retained in a separate category. We also performed a secondary analysis excluding offspring with CHD.

Results

Baseline characteristics for the 1662 offspring participants (51% women) in the study sample are shown in Table 1. For 1059 participants (533 women), a CHD event had occurred in at least one parent. For 725 participants (354 women), the parental CHD event was premature (occurring before age 60 in the parent). Mean internal carotid IMT values were 1.11 ± 0.55 and 1.06 ± 0.51 mm for men with and without premature parental CHD, respectively. Corresponding values in women were 0.91 ± 0.56 and 0.86 ± 0.40 mm.

Adjusted mean internal carotid IMT values for subjects with and without premature parental CHD are shown in Table 2. A validated history of premature parental CHD was associated with a higher age-adjusted internal carotid IMT in both men (1.13 versus 1.04 mm; $P < 0.01$) and women (0.92 versus 0.85 mm; $P = 0.03$). A significant association persisted even after adjustment for other cardiovascular risk factors (Table 2). No significant association was noted between common carotid IMT and premature parental CHD (data not shown).

The above analyses were repeated using logarithmic transformations of the IMT variables and using a generalizing estimating equations model to account for familial correlations. Similar results were obtained, demonstrating a significant association between internal carotid IMT and premature parental CHD (data not shown). Results were also similar in analyses excluding offspring with CHD, and in analyses using a fasting glucose threshold of 126 mg/dL for diabetes rather than 140 mg/dL.

We performed additional analyses taking into account the number and sex of parents having premature CHD. There was no significant difference in mean internal carotid IMT in subjects with premature CHD in both parents ($n = 63$) compared with subjects with premature CHD in only one parent ($n = 662$). There was also no difference in mean internal carotid IMT between subjects with maternal CHD and subjects with paternal CHD.

TABLE 1. Baseline Characteristics

	Premature Parental CHD Status			
	Men		Women	
	Yes (n=371)	No (n=436)	Yes (n=354)	No (n=501)
Mean age, y (range)	56 (37–75)	57 (36–83)	57 (35–78)	58 (34–78)
Mean systolic blood pressure, mm Hg	128	128	126	125
Mean pulse pressure, mm Hg	51	51	52	52
Hypertension therapy, %	29.8	23.2	20.3	23.8
Smoking, %	17.8	13.8	19.2	14.6
Diabetes, %	9.2	8.0	6.8	5.4
Mean body mass index, kg/m ²	28.5	28.4	27.4	27.5
Mean total cholesterol, mg/dL	202	203	216	213
Mean HDL cholesterol, mg/dL	44	44	57	60
Prevalent coronary heart disease, %	8.6	6.4	3.7	3.4

We then examined the association of internal carotid IMT with any parental CHD (ie, no restriction on age of onset). These results are shown in Table 3. In men, the age-adjusted mean internal carotid IMT was higher in subjects with parental CHD than in those without parental CHD (1.11 versus 1.02 mm; $P=0.01$). This association was attenuated after adjustment for offspring blood pressure ($P=0.06$), but not after adjustment for cholesterol or other variables. In

women, there was a nonsignificant trend toward increased internal carotid IMT in those with a positive parental history compared with those without a parental history in each of the models (age-adjusted mean IMT 0.90 versus 0.84 mm; $P=0.05$). In the full multivariable models, no significant association was noted between internal carotid IMT and any parental CHD (Table 3). Furthermore, there was no association between common carotid IMT and any parental CHD (data not shown).

TABLE 2. Mean Internal Carotid IMT in Millimeters (SE), by Parental Premature (age <60) CHD Status

Adjustment	Men (n=800)	Women (n=842)
Age adjusted		
Neither parent	1.04 (0.02)	0.85 (0.02)
At least one parent	1.13 (0.03)*	0.92 (0.02)*
Age+blood pressure variables‡		
Neither parent	1.05 (0.02)	0.85 (0.02)
At least one parent	1.13 (0.03)*	0.92 (0.02)*
Age+cholesterol variables§		
Neither parent	1.04 (0.02)	0.85 (0.02)
At least one parent	1.13 (0.03)*	0.91 (0.02)*
Age+other variables		
Neither parent	1.05 (0.02)	0.85 (0.02)
At least one parent	1.13 (0.03)*	0.92 (0.02)*
Fully adjusted		
Neither parent	1.05 (0.02)	0.85 (0.02)
At least one parent	1.12 (0.03)*	0.92 (0.02)*

Values represent IMT after adjustment for variables in the first column, with standard errors in parentheses. CHD events occurring at or after age 60 are not counted in the classification of parental premature disease status. Internal carotid IMT includes the proximal internal carotid artery and carotid bulb IMT. Internal carotid IMT measurement not available in 20 subjects.

* $P<0.05$, when compared with Neither Parent group.

‡Systolic blood pressure, pulse pressure, and use of antihypertensive therapy.

§Total and HDL cholesterol.

||Smoking, body mass index, and diabetes.

TABLE 3. Mean Internal Carotid IMT in Millimeters (SE), by Parental CHD Status

Adjustment	Men (n=800)	Women (n=842)
Age adjusted		
Neither parent	1.02 (0.03)	0.84 (0.02)
At least one parent	1.11 (0.02)*	0.90 (0.02)†
Age+blood pressure variables‡		
Neither parent	1.04 (0.03)	0.85 (0.02)
At least one parent	1.10 (0.02)†	0.89 (0.02)
Age+cholesterol variables§		
Neither parent	1.02 (0.03)	0.84 (0.02)
At least one parent	1.11 (0.02)*	0.89 (0.02)†
Age+other variables		
Neither parent	1.04 (0.03)	0.84 (0.02)
At least one parent	1.11 (0.02)*	0.90 (0.02)†
Fully adjusted		
Neither parent	1.04 (0.03)	0.85 (0.02)
At least one parent	1.10 (0.02)	0.89 (0.02)

Values represent IMT after adjustment for variables in the first column, with standard errors in parentheses. Internal carotid IMT includes the proximal internal carotid artery and carotid bulb IMT. Internal carotid IMT measurement not available in 20 subjects.

* $P<0.05$, when compared with Neither Parent group.

† $P<0.10$ when compared with Neither Parent group.

‡Systolic blood pressure, pulse pressure, and use of anti-hypertensive therapy.

§Total and HDL cholesterol.

||Smoking, body mass index, and diabetes.

Discussion

Premature parental CHD was associated with offspring carotid IMT in this large, community-based sample. This association remained significant in risk factor-adjusted analyses, suggesting that the influence of parental CHD is not mediated entirely by traditional cardiovascular disease risk factors. Furthermore, our data are consistent with the concept that premature age of parental disease onset identifies a subgroup with a strong familial predisposition to vascular disease, because IMT differences were smaller and not statistically significant when analyses were expanded to include parental CHD occurring at any age. This observation is consistent with prior studies using clinical endpoints^{6,23} and supports the focus on premature parental CHD in current practice guidelines.²⁵ Later-onset parental CHD may represent a more complex phenotype, eg, influenced less substantially by genetic factors, when compared with premature onset CHD.

Several prior studies have examined the association between familial CHD and carotid atherosclerosis. In a biracial sample from the Atherosclerosis Risk in Communities Study, Bensen¹⁰ reported that CHD family risk score was correlated with mean IMT in whites, but not African-Americans. Studies of European cohorts have found associations between carotid thickening or plaque and premature parental CHD death,¹⁶ premature parental myocardial infarction,¹⁷ and premature parental stroke.¹⁷ Related findings have been reported in 2 smaller studies of younger individuals with a family history of myocardial infarction.^{7,26} For instance, Gaeta and colleagues performed ultrasound of the common carotid and brachial arteries in 40 offspring (mean age 19 years) recruited from patients hospitalized with premature acute myocardial infarction.⁷ Compared with age- and sex-matched controls, the offspring had increased common carotid IMT and more abnormalities in brachial artery reactivity.

An important advantage of the present study compared with prior epidemiological reports is the method of ascertaining parental disease history. In previous studies, parental disease status was based on the report of the offspring, without validation. Inaccuracies in offspring-reported parental history have been documented by prior investigators.^{27,28} This introduces the possibility of recall bias, because offspring with a personal history of cardiovascular disease risk factors may be more cognizant of their parents' cardiovascular history. In the Framingham Heart Study, all cardiovascular endpoints in the original and offspring cohorts have been adjudicated in a standardized manner, as they occurred, and uniform diagnostic criteria applied by a physician panel. Thus, the information on cardiovascular events used in the present study was collected prospectively and not based on a retrospective offspring report.

It is also worth noting that subjects in the original cohort have been followed for 5 decades, which further minimizes the risk of misclassification. We have complete ascertainment of premature CHD events in parents (all of whom are currently over age 65) and near-complete ascertainment of later CHD events, as fewer than 15% in the parental cohort remain alive.

We examined the association between parental CHD and offspring IMT before and after adjustment for cardiovascular disease risk factors. Understanding whether the familial predis-

position for CHD is explained by established risk factors, such as blood pressure or cholesterol, may provide clues regarding mechanisms.^{29,30} For instance, although the association between premature parental CHD and offspring IMT remained significant after full multivariable adjustment, blood pressure variables attenuated this relation, suggesting that blood pressure may lie in the etiological pathway. It is important to note that we adjusted only for concurrent risk factor levels; past levels of risk factors may also contribute to atherosclerosis. Although concurrent risk factors appear to correlate reasonably with past risk factors,³¹ additional studies that account for risk factor tracking in individuals with and without parental CHD may provide further insight into the relations between parental history, traditional risk factors, and atherosclerosis.

We also analyzed the internal and common carotid artery segments separately, because of the site-specific nature of carotid atherosclerosis³² and the observation that determinants of carotid IMT may differ between sites.¹³ Internal carotid/bulb IMT may be a better marker of focal atherosclerosis than common carotid IMT, because plaques have a tendency to form near areas of nonlaminar flow.^{13,33} The importance of hemodynamic factors in the distribution of carotid atherosclerosis is supported by animal models.³⁴ Prospective studies have found internal carotid IMT to be a better predictor of cardiac events than common carotid IMT.¹⁵ Our finding that internal carotid IMT is associated with parental disease history in this middle-aged cohort is consistent with the hypothesis that the familial predisposition for CHD is mediated, at least in part, by subclinical atherosclerosis.

Several limitations of our study should be acknowledged. Our sample was restricted to offspring who had both parents in the original Framingham cohort. Parents who died at a very young age from CHD may have been less likely to be included in the original study. Nonetheless, recruitment for the original cohort began when most parents were young and unlikely to have a significant CHD history.

We viewed carotid IMT as a marker for subclinical atherosclerosis. Although the significance of carotid thickening, particularly in the distal common carotid artery, continues to be debated, its association with prevalent and future CHD has been supported by a number of studies. O'Leary and colleagues have shown that submillimeter differences in carotid IMT, as observed in our study, are prognostically important.¹⁵ Nonetheless, it should be acknowledged that atherosclerosis may progress in other vascular beds, including the coronary circulation, at different rates. The results of this study may not apply to atherosclerosis in other major vascular territories. Interestingly, an association between coronary intimal thickening and a family history of CHD has been described by Kaprio and colleagues,³⁵ who studied infant autopsy specimens.

Additionally, further work is needed to elucidate the clinical utility of our findings. Despite the positive results, there is substantial overlap in the distribution of IMT among those with and without a family history, with there being a wide range of observed values in both groups. On the basis of prior research, it is apparent that the individual patient with either elevated carotid IMT¹⁵ or a premature family history^{6,23} is at increased risk for cardiovascular events. However,

whether these characteristics add sufficient independent predictive value to warrant widespread use of carotid ultrasound in those with a positive family history requires further study.

In conclusion, we found an association between parental premature CHD and offspring carotid IMT in this large, prospective family-based cohort. Our results and those of prior studies strongly support the existence of anatomic and functional vascular abnormalities in offspring of parents with premature CHD, independent of known vascular risk factors.^{7,10,36,37} Further investigation may help to clarify the relative contribution of shared genetic background versus shared environmental influences to this familial predisposition. In this regard, carotid IMT may be a useful phenotype for the study of the genetic transmission of CHD.

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Correction

The article, “Carotid Intima-Media Thickness Is Associated With Premature Parental Coronary Heart Disease: The Framingham Heart Study” by Wang et al that appeared in the August 5, 2003, issue (*Circulation*. 2003;108:572-576) contained an error. Because of a programming error, the age cutoff used to define premature coronary heart disease was 70 years, rather than 60 years as stated in the Methods (fourth paragraph) and the title of Table 2. The corrected title for Table 2 should read, “Table 2: Mean Internal Carotid IMT in mm (Standard Error), by Parental Premature (Age <70) CHD Status.”

If age 60 years is used rather than 70 years, the results do not change in men (age-adjusted internal carotid intima-media thickness [IMT] in those with versus without premature parental coronary heart disease [CHD], 1.17 vs. 1.05 mm, $P=0.003$) but are slightly attenuated in women (age-adjusted internal carotid IMT in those with versus without premature parental CHD, 0.92 vs. 0.86 mm, $P=0.13$).

The authors regret this error and any confusion it may have caused.

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